PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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GRANDE BRETAGNE

PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	30.03.2004
Applicant's or agent's file reference	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/02942	07.07.2003	10.07.2002

International Patent Classification (IPC) or both national classification and IPC
C12N9/74, C12N9/74

Applicant
NATIONAL BLOOD AUTHORITY et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: Last of 28 mos epd = 10-11-04
6 mos from Demand = July '04

Name and mailing address of the international preliminary examining authority:

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Authorized Officer

Formalities officer (incl. extension of time limits)
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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-32 as originally filed

Claims, Numbers

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	9-13
Inventive step (IS)	Claims	1-13
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: EP-A-0 543 178 (BEHRINGWERKE AG) 26 May 1993 (1993-05-26)
D2: EP-A-0 439 156 (WARNER LAMBERT POTTERY ROAD LI) 31 July 1991
D3: EP-A-1 136 084 (AVENTIS BEHRING GMBH) 26 September 2001
D4: WO 00/71153 A (BIO PROD & BIO ENG AG ;EIBL JOHANN (AT)) 30 November 2000 (2000-11-30)
D5: EP-A-0 565 511 (IMMUNO AG) 13 October 1993 (1993-10-13)
D6: GOLDSACK NEIL ET AL: "Molecules in focus thrombin" INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY, vol. 30, no. 6, June 1998 (1998-06), pages 641-646

Additional document:
D7: EP1161958

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty (Art. 33(2) PCT)

The application relates to a method for the preparation of virus-inactivated thrombin comprising solvent-detergent virus inactivation of a solution comprising prothrombin and factor X, loading the virus inactivated prothrombin and factor X onto an anion exchange medium, washing the medium to remove the reagents used for the solvent-detergent virus inactivation, and activating the prothrombin on the medium to form thrombin by the addition of metal ions, preferably calcium ions. The thrombin is then preferably selectively eluted from the anion exchange medium.

1.1 The applicant's attention is drawn to the fact that product by process claims as

defined in claims 9-11 and 12-13 will not be admissible in the European regional phase. Such claims are admissible only if the product (thrombin in the present case) by itself fulfil the requirements for patentability and there is no other information available in the application which could enable the applicant to define the product satisfactorily by reference to its composition, structure or some other testable parameter. Thrombin is a well known and studied protein which can be prepared using various methods as disclosed in the prior art D1-D4. The applicant's attention is drawn to the fact that a product is not rendered novel merely by the fact that it is purified by means of a new process.

At present, all applications such as D1-D4 disclosing thrombin (and its obtention/preparation) or pharmaceutical composition/kit comprising thrombin are prejudicial for the novelty of claims 9-13 under Art 33(3) PCT.

2. Inventive step (Art. 33(3) PCT)

The application relates to a method for the preparation of virus-inactivated thrombin comprising solvent-detergent virus inactivation of a solution comprising prothrombin and factor X.

The available prior art D1-D3 relate to the preparation of thrombin free of viral contaminant based on various method/process.
D1 relates to a purified thrombin preparation free from viral contamination. The method comprises treating a solution of prothrombin complex, which has been purified on an ion exchanger and subjected to virus inactivation, with a soluble salt containing an anion.
Another example is D2 which discloses a process for the production of a liquid thrombin preparation which comprises reacting each unit of prothrombin with less than 50% of the conventional thromboplastin input in the presence of calcium, contacting the resultant thrombin with a phosphate buffer, and diluting and filtering the suspension. The filtrate is then applied sequentially to an anion-exchange agarose column and a cation-exchange agarose column and the thrombin fraction is step-wise eluted from the latter column with phosphate buffered saline.

Based on the teaching of the prior art such as D1 or D2, the technical problem to be solved could be seen as the provision of an alternative method for producing a virus inactivated thrombin preparation.

As seen from D1-D4, protein preparation can be treated using different virus inactivation processes. Other methods are known to the skilled person in the art such as solvent-detergent virus inactivation steps. For example, D7 discloses a method for inactivating viruses in biological liquid solution which comprises contacting the biological liquid solution with solvent detergent mixture. The solvent detergent mixture at a predetermined concentration and conditions is able to inactivate lipid-coated viruses. The solvent-detergent mixture is removed by passing the liquid solution on a chromatographic packing.

Thus, in the light of (for example) D1 and D7, the person of skill would have sound reasons to expect that the combination of solvent-detergent and anion-exchange chromatography purification steps would produce similar results as the claimed method. Consequently, in absence of a surprising technical effect, the subject-matter of claims 1-13 is merely an obvious combination of known features and is not considered to require an inventive step. The subject-matter which is not directly been anticipated by D1 and D7 does not appear to involve any technical teaching which can be considered as inventive in view of the routine knowledge of a person skilled in the art.